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Empirical likelihood ratio confidence intervals for conditional survival probabilities with right censored data

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In the analysis of survival data, we often encounter situations where the response variable (the survival time) T is subject to right censoring, but the covariates Z are completely observable and are often discrete or categorical. In this article, we construct the empirical likelihood ratio confidence region for conditional survival probabilities based on bivariate data which are subject to right censoring in one coordinate and have a discrete covariate Z. We show that such an empirical likelihood ratio confidence region is indeed an interval, and we establish some related properties of the empirical likelihood ratio. The generalization of our results in this article to the multivariate covariate Z with dimension $p > 1$ is straightforward.

Keywords and phrases: Empirical likelihood, Maximum likelihood estimator, Right censored data.

1. INTRODUCTION

In the analysis of survival data, we often encounter situations where the response variable is the survival time T and is subject to right censoring, but the p-dimensional vector Z of covariates with components such as treatments, gender, etc., are completely observable. In the nonparametric setting, we are interested in an interval estimate for conditional survival probability $P\{T > t_0 \mid Z = z_0\}$, where t_0 and z_0 are given values of interest. Such a problem is equivalent to constructing confidence intervals for the following conditional probability:

$$\theta_0 = P\{T \le t_0 \mid Z = z_0\}. \tag{1.1}$$

For simplicity of presentation, here we consider the case that covariate Z is a scalar rather than a vector, i.e., Z with dimension $p = 1$. The generalization of our results in this article to the multivariate case with $p > 1$ is straightforward.

Specifically, suppose that

$$(T_1, Z_1), (T_2, Z_2), \ldots, (T_n, Z_n) \tag{1.2}$$

is a random sample of (T, Z), but the actually observed survival data are the bivariate data with one coordinate subject to random right censoring as follows:

$$(V_1, \delta_1, Z_1), (V_2, \delta_2, Z_2), \ldots, (V_n, \delta_n, Z_n), \tag{1.3}$$

where $V_i = \min\{T_i, C_i\}$, $\delta_i = I\{T_i \le C_i\}$, and C_i is the right censoring variable with distribution function (d.f.) F_C and is independent of (T_i, Z_i). Note that in practical situations the covariate variable Z in (1.1)–(1.3) is often discrete or categorical. In this article, we construct *empirical likelihood ratio confidence intervals* (ELRCI) for conditional probability θ_0 in (1.1) based on right censored survival data (1.3), where covariate Z is discrete.

The empirical likelihood approach (Owen, 1988) is a nonparametric likelihood method, thus it is an appealing procedure with broad applications in survival data analysis. We refer to Owen (2001) and a nice survey paper by Li, Li and Zhou (2005) for results on this topic. Among existing works in the literature, the one most closely related to ours is that by Li and van Keilegom (2002), where they constructed confidence intervals and bands for the conditional survival probabilities using the empirical likelihood approach. However, the problem considered by Li and van Keilegom (2002) was for a continuous covariate Z, and their procedure involves bandwidth selection and kernel selection. In comparison, the problem we consider in this article is of special importance in practice, and our procedure does not involve any bandwidth or kernel selection.

The rest of this article is organized as follows. In Section 2, we construct the empirical likelihood based confidence region for θ_0 in (1.1) using the empirical likelihood based *bivariate nonparametric maximum likelihood estimator* (BNPMLE) $\hat{F}_n(t, z)$ for bivariate distribution function (d.f.) $F_0(t, z)$ of (T, Z) with right censored survival data (1.3), which was obtained by Ren and Riddlesworth (2012). We show that such a confidence region is indeed an interval. The proofs are given in Section 3.

It should be noted that the results similar to our main theorems in Section 2 are known for empirical likelihood inference in the univariate data case, however they are not obvious and quite difficult for the case with censored bivariate data which we consider in this paper. Moreover, the computation of ELRCI and the proof of related Wilk's theorem

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are very difficult problems technically, and further careful and much more involved work is needed.

2. EMPIRICAL LIKELIHOOD RATIO CONFIDENCE INTERVALS

To derive the empirical likelihood function for bivariate d.f. $F_0(t,z)$ of (T,Z) based on survival data (1.3), we let all possible values of discrete covariate variable Z be given by:

$$z_1, z_2, \ldots \tag{2.1}$$

and let

(2.2)
$$\begin{array}{ll} U_1 < \cdots < U_m & \text{be all distinct values among } V_1, \ldots, V_n; \\ Y_1 < \cdots < Y_q & \text{be all distinct values among } Z_1, \ldots, Z_n. \end{array}$$

Denoting

$$\begin{aligned} n_{ij} &= \sum_{k=1}^{n} I\{V_k = U_i, Z_k = Y_j\}, \\ \delta_{ij} &= \sum_{k=1}^{n} I\{V_k = U_i, \delta_k = 1, Z_k = Y_j\} \end{aligned} \tag{2.3}$$

for $1 \le i \le m$, $1 \le j \le q$, Ren and Riddlesworth (2012) show that the likelihood function for bivariate distribution function $F_0(t,z)$ of (T,Z) with data (1.3) is given by

$$\begin{aligned} L(F) = \prod_{i=1}^{m}\prod_{j=1}^{q} &(dF(U_i, Y_j))^{\delta_{ij}} \\ &\times (F(\infty, dz_j) - F(U_i, dY_j))^{n_{ij}-\delta_{ij}}, \end{aligned} \tag{2.4}$$

where F is any bivariate d.f., and denoting P_F as the probability under F we have:

(2.5)
$$\begin{cases} dF(t,z) = P_F\{T = t, Z = z\} \\ F(t, dz) = P_F\{T \le t, Z = z\} = F(t,z) - F(t, z-). \end{cases}$$

In order to derive the ELRCI for θ_0 in (1.1), we first describe the BNPMLE $\hat{F}_n(t,z)$ for $F_0(t,z)$ by Ren and Riddlesworth (2012) as follows.

Note that (2.3) implies $n_{1j} + \cdots + n_{mj} \ge 1$ for any $1 \le j \le q$ and that $n_{ij} = 0$ implies $\delta_{ij} = 0$. Thus, letting

$$m_j = \max\{k \mid n_{kj} > 0\}, \quad 1 \le j \le q \tag{2.6}$$

we have $n_{ij} = \delta_{ij} = 0$ for all $1 \le j \le q$, $m_j < i \le m$; which means that points (U_i, Y_j) for $m_j < i \le m$ are not observed among (V_k, Z_k)'s in data (1.3), in turn, by the usual empirical likelihood treatment these points (U_i, Y_j) are not assigned any probability masses. Hence, to find the BNPMLE for F_0 with likelihood function (2.4), Ren and Riddlesworth (2012) restrict all possible candidates to those bivariate d.f.'s that assign all their probability masses to points (U_i, Y_j) for $1 \le j \le m$, $1 \le i \le m_j$ and line segments $L_j = \{(t, Y_j) \in \mathbb{R}^2;\ t > U_m\}$ for $1 \le j \le q$, which writes likelihood function (2.4) as follows:

$$L(F) = \prod_{j=1}^{q}\prod_{i=1}^{m} (p_{ij})^{\delta_{ij}} \left(\sum_{k=i+1}^{m+1} p_{kj}\right)^{n_{ij}-\delta_{ij}} \equiv L(\boldsymbol{p}), \tag{2.7}$$

where

(2.8)
$$F(t,z) = \sum_{i=1}^{m}\sum_{j=1}^{q} p_{ij} I\{U_i \le t, Y_j \le z\}, \quad \text{for } t \le U_m,\ z \in \mathbb{R}$$

satisfies

(2.9)
$$\begin{cases} p_{ij} = dF(U_i, Y_j) = P_F\{T = U_i, Z = Y_j\}, \\ \quad \text{for } 1 \le j \le q,\ 1 \le i \le m \\ p_{ij} = 0, \quad \text{for } 1 \le j \le q,\ m_j < i \le m \\ p_{m+1,j} = P_F\{(T,Z) \in L_j\} = P_F\{T > U_m, Z = Y_j\}, \\ \quad \text{for } 1 \le j \le q \\ \displaystyle\sum_{j=1}^{q}\sum_{i=1}^{m+1} p_{ij} = 1. \end{cases}$$

Hence, the BNPMLE $\hat{F}_n(t,z)$ for $F_0(t,z)$ is the solution that maximizes above likelihood function $L(F) = L(\boldsymbol{p})$ in (2.7).

Let $\hat{\boldsymbol{p}}$ denote the solution of the following optimization problem:

$$\begin{cases} \max L(\boldsymbol{p}) = \displaystyle\prod_{j=1}^{q}\prod_{i=1}^{m} (p_{ij})^{\delta_{ij}} \left(\sum_{k=i+1}^{m+1} p_{kj}\right)^{n_{ij}-\delta_{ij}} \\ \text{subject to:} \quad \text{Constraints on } \boldsymbol{p} \text{ in (2.9)}. \end{cases} \tag{2.10}$$

Ren and Riddlesworth (2012) show that in the sense of the empirical likelihood method the BNPMLE $\hat{F}_n(t,z)$ for $F_0(t,z)$ is *uniquely* given as stated in the following theorem.

Theorem 1. *For any $1 \le i \le m$, $1 \le j \le q$, we denote*

$$N_{ij} = n_{ij} + \cdots + n_{mj} = \sum_{k=1}^{n} I\{V_k \ge U_i, Z_k = Y_j\}. \tag{2.11}$$

Then, the solution $\hat{\boldsymbol{p}}$ of (2.10) is unique and satisfies the following:

(i) For any $1 \le j \le q$, $1 \le i \le m_j$, we have $\hat{p}_{ij} > 0$ if and only if $\delta_{ij} > 0$;

(ii) For any $1 \le j \le q$, $1 \le i \le m_j$, we have $\sum_{k=i}^{m+1} \hat{p}_{kj} > 0$;

(iii) *With notation $\prod_{k=1}^{0} c_k \equiv 1$, the BNPMLE $\hat{F}_n(t,z)$ is given by*

(2.12)
$$\begin{cases} \hat{F}_n(t,z) = \sum_{i=1}^{m}\sum_{j=1}^{q} \hat{p}_{ij} I\{U_i \le t, Y_j \le z\}, \\ \quad \textit{for } t \le U_m,\ z \in \mathbb{R} \\ \hat{p}_{ij} = \left(\frac{\delta_{ij}}{N_{ij}}\right)\left(\frac{N_{1j}}{n}\right)\prod_{k=1}^{i-1}\left(1-\frac{\delta_{kj}}{N_{kj}}\right), \\ \quad \textit{for } 1 \le i \le m,\ 1 \le j \le q \\ \hat{p}_{m+1,j} = P_{\hat{F}_n}\{T > U_m, Z = Y_j\} = \left(\frac{N_{1j}}{n}\right) - \sum_{i=1}^{m}\hat{p}_{ij}, \\ \quad \textit{for } 1 \le j \le q \end{cases}$$

where $0/0$ is set as 0 whenever it occurs.

One should note that (2.3), (2.6) and (2.11) imply that for any $1 \le j \le q$,

(2.13)
$$\begin{cases} n_{m_j,j} > 0 \Rightarrow N_{1j} \ge N_{2j} \ge \cdots \ge N_{m_j,j} > 0 \\ n_{ij} = \delta_{ij} = N_{ij} = 0, \quad \text{for } m_j < i \le m \text{ when } m_j < m. \end{cases}$$

Thus, constraint on $\boldsymbol{p}$ in the second line of (2.9) is satisfied in (2.12).

To construct ELRCI for θ_0 in (1.1), we define the following statistical functional:

$$\tau(F) = P_F\{T \le t_0 \mid Z = z_0\} \tag{2.14}$$

where F is given by (2.8)–(2.9). Since covariate variable Z is discrete and z_0 is a value of interest for Z, then z_0 must be one of the values in (2.1), and from $0 < F_Z(z_0) < 1$ and Theorem 4.2.1 of Chung (1974) there exists integer ζ in (2.2) such that

(2.15)
$$Y_\zeta = z_0 \quad \text{for } 1 \le \zeta \le q, \text{ almost surely except finitely often.}$$

Similarly, under assumption of $0 < F_V(t_0) < 1$ for d.f. F_V of V in (1.3), from Theorem 4.2.1 of Chung (1974) we have that in (2.2) almost surely except finitely often,

$$t_0 < U_m. \tag{2.16}$$

Thus, from (2.8)–(2.9) and (2.15)–(2.16) we can write (2.14) as

(2.17)
$$\tau(F) = \frac{P_F\{T \le t_0, Z = z_0 = Y_\zeta\}}{P_F\{T \le U_m, Z = Y_\zeta\} + P_F\{T > U_m, Z = Y_\zeta\}} = \frac{\sum_{i=1}^{m} p_{i\zeta} I\{U_i \le t_0\}}{\sum_{i=1}^{m+1} p_{i\zeta}} \equiv \tau(\boldsymbol{p}).$$

For likelihood function (2.7) and the BNPMLE $\hat{F}_n$ given by (2.12), we know that the empirical likelihood ratio is given by $R(F) = L(F)/L(\hat{F}_n)$ and we denote

$$r(\theta) = \sup_F\{R(F) \mid \tau(F) = \theta\} = (L(\hat{F}_n))^{-1}\sup_{\boldsymbol{p}}\{L(\boldsymbol{p}) \mid \tau(\boldsymbol{p}) = \theta\}. \tag{2.18}$$

Then, for constant $0 < c < 1$ the empirical likelihood ratio confidence set S_n for conditional probability θ_0 in (1.1) is given by

$$S_n = \{\tau(F) \mid R(F) \ge c\} = \{\tau(\boldsymbol{p}) \mid \boldsymbol{p} \in \mathcal{E}_n\} \tag{2.19}$$

where $\mathcal{E}_n = \{\boldsymbol{p} \mid \boldsymbol{p} \text{ satisfies (2.8)–(2.9) and } L(\boldsymbol{p}) \ge cL(\hat{F}_n)\}$. With the proofs deferred to Section 3, we have the following theorems on above confidence set S_n.

Theorem 2. *Confidence set S_n in (2.19) is an interval satisfying $S_n = [T_L, T_U]$ with*

$$T_L = \min_{\boldsymbol{p}\in\mathcal{E}_n} \tau(\boldsymbol{p}) \quad \textit{and} \quad T_U = \max_{\boldsymbol{p}\in\mathcal{E}_n} \tau(\boldsymbol{p}). \tag{2.20}$$

Theorem 3. *For $r(\theta)$ and S_n given by (2.18) and (2.19), respectively, we have*

$$\theta_0 \in S_n \quad \textit{if and only if} \quad r(\theta_0) \ge c. \tag{2.21}$$

Remark 1. The results similar to above Theorem 2 and Theorem 3 are known for empirical likelihood inference in the univariate data case, however they are not obvious for the case with censored bivariate data which we consider in this current paper. In fact, the proofs are quite involved technically as shown in Section 3 as well as in Ren and Riddlesworth (2012). The computation of ELRCI $[T_L, T_U]$ given in (2.20) is also a quite difficult problem; see Riddlesworth (2011) for discussions and partial solutions on this topic. For the empirical likelihood ratio $r(\theta_0)$ given by (2.18), we expect Wilk's theorem to hold, but the proof turns out to be very difficult in this case. For such a proof, further careful and much more involved technical work is needed, while results (2.21) in Theorem 3 is useful in this context and can be used to set constant c in practice.

3. PROOFS

Proof of Theorem 2. Note that set $\mathcal{E}_n$ in (2.19) is compact, because $L(\boldsymbol{p})$ in (2.7) is continuous in $\boldsymbol{p}$. Also, note that (2.6) and $L(\boldsymbol{p}) \ge cL(\hat{F}_n) > 0$ imply the following in the product of $L(\boldsymbol{p})$ given by (2.7):

$$0 < (p_{m_j,j})^{\delta_{m_j,j}}\left(\sum_{k=m_j+1}^{m+1} p_{kj}\right)^{n_{m_j,j}-\delta_{m_j,j}},$$

in turn, from $n_{m_j,j} > 0$ in (2.13), we have $\sum_{k=m_j+1}^{m+1} p_{kj} > 0$ when $\delta_{m_j,j} = 0$; $p_{m_j,j} > 0$ when $\delta_{m_j,j} > 0$; which give

$\sum_{k=m_j}^{m+1} p_{_{kj}} > 0$ for any $1 \le j \le q$. Thus, we have

$$\text{(3.1)} \qquad \boldsymbol{p} \in \mathcal{E}_n \Rightarrow \sum_{k=i}^{m+1} p_{_{kj}} > 0 \Rightarrow \sum_{k=1}^{m+1} p_{_{kj}} > 0$$

for any $1 \le j \le q$, $1 \le i \le m_j$. Hence, $\tau(\boldsymbol{p})$ in (2.17) is well-defined and continuous on compact set $\mathcal{E}_n$ given in (2.19), which, from Royden (1988; page 191), implies S_n is compact.

From (2.6) and (2.13), we define the following transformation function:

$$\text{(3.2)} \qquad h(\boldsymbol{p}) = (\boldsymbol{a}, \boldsymbol{b}) \quad \text{for} \begin{cases} a_{ij} = p_{_{ij}}/b_{ij} \\ b_{ij} = \sum_{k=i}^{m+1} p_{_{kj}} \end{cases} \quad 1 \le j \le q,\ 1 \le i \le m_j,$$

where $\boldsymbol{a} = (a_{ij})$ and $\boldsymbol{b} = (b_{1j})$. Note that from (3.1), $h(\boldsymbol{p})$ is well-defined on $\mathcal{E}_n$, and that by iteration on (3.2), it can be shown that h^{-1} uniquely exists and is continuous. With some algebraic work, Ren and Riddlesworth (2012) establish the following for $L(\boldsymbol{p})$ in (2.7):

$$\text{(3.3)} \qquad \begin{aligned} L(\boldsymbol{p}) &= L(h^{-1}(\boldsymbol{a}, \boldsymbol{b})) \\ &= \left(\prod_{j=1}^{q} (b_{1j})^{N_{1j}}\right) \left(\prod_{j=1}^{q} \prod_{i=1}^{m_j} (a_{ij})^{\delta_{ij}} (1 - a_{ij})^{N_{ij} - \delta_{ij}}\right) \\ &\equiv G(\boldsymbol{a}, \boldsymbol{b}), \end{aligned}$$

which, from (3.1)–(3.2) and (2.8)–(2.9), implies

$$\text{(3.4)} \qquad \begin{aligned} h(\mathcal{E}_n) &= \{h(\boldsymbol{p}) \mid L(\boldsymbol{p} \ge cL(\hat{F}_n)\} \\ &= \{(\boldsymbol{a}, \boldsymbol{b}) \mid (\boldsymbol{a}, \boldsymbol{b}) \in \mathcal{F}_n, G(\boldsymbol{a}, \boldsymbol{b}) \ge cL(\hat{F}_n)\} \end{aligned}$$

where

$$\text{(3.5)} \qquad \mathcal{F}_n = \left\{ (\boldsymbol{a}, \boldsymbol{b}) \mid 0 \le a_{ij} \le 1, 0 < b_{1j} < 1 \right. \\ \left. \text{for } 1 \le j \le q, 1 \le i \le m_j;\ \sum_{j=1}^{q} b_{ij} = 1 \right\}.$$

Since $\log G(\boldsymbol{a}, \boldsymbol{b})$ is concave down, we know that from Bazaraa et al. (1993; page 116), $G(\boldsymbol{a}, \boldsymbol{b})$ is quasiconcave (see definition in Bazaraa et al., 1993; page 108). Thus, if

$$G(\boldsymbol{a}^{(1)}, \boldsymbol{b}^{(1)}) \ge cL(\hat{F}_n) \quad \text{and} \quad G(\boldsymbol{a}^{(2)}, \boldsymbol{b}^{(2)}) \ge cL(\hat{F}_n),$$

we have that for any $0 \le \lambda \le 1$,

$$\begin{aligned} &G(\lambda(\boldsymbol{a}^{(1)}, \boldsymbol{b}^{(1)}) + (1 - \lambda)(\boldsymbol{a}^{(2)}, \boldsymbol{b}^{(2)})) \\ &\quad \ge \min\{G(\boldsymbol{a}^{(1)}, \boldsymbol{b}^{(1)}), G(\boldsymbol{a}^{(2)}, \boldsymbol{b}^{(2)})\} \ge cL(\hat{F}_n). \end{aligned}$$

Hence, $h(\mathcal{E}_n)$ in (3.4) is convex due to (3.5).

From Royden (1988; page 183, Problem 35), we know that the convexity of $h(\mathcal{E}_n)$ implies that $h(\mathcal{E}_n)$ is connected. Thus, the continuity of h^{-1} implies $h^{-1}(h(\mathcal{E}_n)) = \mathcal{E}_n$ is connected; in turn, S_n is connected due to continuity of $\tau(\boldsymbol{p})$ (Royden, 1988; page 182). From Royden (1988; page 183), we know that S_n is either an interval or a single point. Since S_n is compact and since $\tau(\boldsymbol{p})$ is continuous on compact set $\mathcal{E}_n$, we know that S_n is a closed interval $[T_L, T_U]$ with T_L and T_U given by (2.20). □

Proof of Theorem 3. Assume $\theta_0 \in S_n = [T_L, T_U]$, where T_L and T_U are given by (2.20). From the proof of Theorem 2, we know that $\tau(\boldsymbol{p})$ in (2.17) is continuous on $\mathcal{E}_n$ in (2.19). Since T_L and T_U are the lower and upper bound of $\tau(\boldsymbol{p})$ on $\mathcal{E}_n$, respectively, we know that from the Intermediate Value Theorem, there exists $\boldsymbol{p}^* \in \mathcal{E}_n$ such that $\theta_0 = \tau(\boldsymbol{p}^*)$. From $\boldsymbol{p}^* \in \mathcal{E}_n$, we know $L(\boldsymbol{p}^*) \ge cL(\hat{F}_n)$, which, from (2.18) and $\theta_0 = \tau(\boldsymbol{p}^*)$, implies

$$r(\theta_0) = (L(\hat{F}_n))^{-1} \sup_{\boldsymbol{p}} \{L(\boldsymbol{p}) \mid \tau(\boldsymbol{p}) = \theta_0\} \ge \frac{L(\boldsymbol{p}^*)}{L(\hat{F}_n)} \ge c.$$

Assume $r(\theta_0) \ge c$, where $r(\theta_0)$ is given by (2.18). From (2.16)–(2.17), we know that

$$\text{(3.6)} \qquad E_n = \{\boldsymbol{p} \mid \boldsymbol{p} \text{ satisfies (2.8)–(2.9) and } \tau(\boldsymbol{p}) = \theta_0\}$$

is not empty. Thus, from (2.18) there exists a sequence of points $\boldsymbol{p}^{(k)} \in E_n$ such that

$$\text{(3.7)} \qquad \frac{L(\boldsymbol{p}^{(k)})}{L(\hat{F}_n)} \ge r(\theta_0) - \frac{1}{k}$$

for sufficiently large k. Since (3.6)–(3.7) and $r(\theta_0) \ge c$ imply

$$\text{(3.8)} \qquad \tau(\boldsymbol{p}^{(k)}) = \theta_0 \quad \text{and} \quad \frac{L(\boldsymbol{p}^{(k)})}{L(\hat{F}_n)} \ge c - \frac{1}{k},$$

and since $\{\boldsymbol{p}^{(k)}\}$ contains a convergent subsequence, still denoted as $\{\boldsymbol{p}^{(k)}\}$, such that

$$\text{(3.9)} \qquad \boldsymbol{p}^{(k)} \to \boldsymbol{p}^{(0)}, \quad \text{as } n \to \infty$$

where $\boldsymbol{p}^{(0)}$ satisfies (2.8)–(2.9), we know that the continuity of $L(\boldsymbol{p})$ in (2.7) gives

$$\text{(3.10)} \qquad \frac{L(\boldsymbol{p}^{(0)})}{L(\hat{F}_n)} = \lim_{k \to \infty} \frac{L(\boldsymbol{p}^{(k)})}{L(\hat{F}_n)} \ge c > 0.$$

Note that from the arguments in (3.1), above (3.10) implies $\sum_{i=1}^{m+1} p_{_{i\varsigma}}^{(0)} > 0$. Thus, from (2.17) and (3.8)–(3.9) we have

$$\text{(3.11)} \qquad \tau(\boldsymbol{p}^{(0)}) = \lim_{k \to \infty} \tau(\boldsymbol{p}^{(k)}) = \theta_0.$$

The proof follows from (2.19) and (3.9)–(3.11). □

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